

Appl. No. : 09/991,721
Filed : November 13, 2001

REMARKS

Claims 1-13, 15, 17, 18, 25, and 45-50 are pending in this application. Amendments to the claims: None. Reexamination and reconsideration of the application, as amended, are respectfully requested.

A. Compliance with 35 USC 103(a)

The U.S. Patent and Trademark Office (USPTO) rejected the claims under 35 USC 103(a) as being unpatentable over Mastrangelo et al. (1995) WO 95/31105 in view of Dorner et al. USP 6,103,244 and further in view of Buller et al. (1988) J Virol 62: 866; additional claims further in view of Zhang et al. (1996) Biochem Biophys Res Commun 227: 707; and further claims further in view of Paoletti USP 5,942,235 (as further evidenced by P04637).

The rule according to MPEP 2143 is that when an invention is contended to be obvious based upon a combination of elements from different prior art references, there must be a suggestion, motivation, or teaching to those skilled in the art for such a combination.

Attached is Declaration under 37 CFR 1.132 of Richard C. Condit, Ph.D. Dr. Condit is an expert in the science of vaccinia viruses. As required under MPEP 716.01 II, Dr. Condit is a third party signatory to place evidence in the record attacking or rebutting any prima facie case of obviousness.

Regarding the references cited therein: Child et al. 1990 and Tartaglia et al. 1992 are submitted herewith in an Information Disclosure Statement (IDS). All other references are of record.

The invention is a combined thymidine kinase-deleted (TK-) and vaccinia growth factor-deleted (VGF-) vaccinia virus. Condit Decl. ¶ 4. The invention would not have been obvious at the time of the May 1999 filing date, not even in view of the combination of the closest prior art, Buller et al. 1985 and Buller et al. 1988, not even on the reasoning that it would be desirable to combine the two safety mutations to achieve reduced virulence. Id. Buller et al. 1985 describes a thymidine kinase-deleted (TK-) vaccinia virus. Id. Buller et al. 1988 describes a vaccinia growth factor-deleted (VGF-) vaccinia virus. Id.

Appl. No. : 09/991,721
Filed : November 13, 2001

There is more to this than just combining two SAFETY mutations. Condit Decl. ¶ 5. The double deletion has the ability to selectively replicate in tumor tissues compared with normal tissues and is thus tumor-selective. Id. In neither case of Buller et al. 1985 nor Buller et al. 1988 is there any mention of tumor specificity. Condit Decl. ¶ 6.

There are many other possible “safety” mutations, as discussed in Tartaglia et al. 1992. Condit Decl. ¶ 7. While combinations of these safety mutations might result in reduced virulence, additivity is empirical. Id. A combined effect of a double deletion was speculative and could not have been predicted. Id.

It may be true that, knowing the prior art, one has the potential for hypothesizing a combination of virulence genes. Condit Decl. ¶ 9. Nevertheless, because of the quantity of virulence genes, there are a vast number of combinations. Id.

The rule according to MPEP 2144.08 II A 4 (a) is that the size of the genus must be considered when determining whether one would have been motivated to select the claimed species. In the case of Paoletti et al. (1992) WO 92/15672, in which 38 ORFs were deleted to make NYVAC.2, there are a possibility of 703 double deletions. Condit Decl. ¶ 9. There was no motivation to select the TK and VGF ORFs from among these possibilities. Id.

Given the enormous number of possibilities suggested by the prior art, and the failure of the prior art to suggest which of those possibilities is the claimed combination, the TK- and VGF- double deletion would not have been obvious. Id.

The rule according to MPEP 2141.02 is that a case of prima facie obviousness cannot be established if it can be shown that the prior art teaches away from the claimed invention. In prior art experiments, the thymidine kinase-deleted and ribonucleotide reductase-deleted vaccinia virus double deletion was not as attenuated as might have been predicted from the data with the two single deletions, and therefore this teaches away from the idea that the effects of combination of any two safety mutations is predictable and obvious. Condit Decl. ¶ 10.

The rule according to MPEP 716.02 is that a case of prima facie obviousness can be rebutted if it can shown that there are new and unexpected results relative to the prior art. Nothing in the prior art suggested that the double deletion could enhance the tumor specificity of vaccinia virus. Condit Decl. ¶ 11. McCart et al. 2001 cited no pre-filing date publications to

Appl. No. : 09/991,721
Filed : November 13, 2001

support the conclusion that the combination of a TK deletion and a VGF deletion would provide enhanced tumor selectivity. Condit Decl. ¶ 15. The double deletion produces a new and unexpected result of tumor selectivity that is different from the results of the prior art.

Whether considered singly or together, no motivation to select the claimed combination is taught by the cited prior art references, Mastrangelo et al. (1995) WO 95/31105 in view of Dorner et al. USP 6,103,244 and further in view of Buller et al. 1988. Condit Decl. ¶ 20. The rule according to MPEP 2143.01 III is that just because one CAN make a combination does not make the resultant combination obvious. These references do not suggest the desireability of combining the TK and VGF safety mutations to achieve reduced virulence, because a prior art double deletion was merely comparable in replication to the single deletion and only the deletion of multiple virulence genes provided a highly attenuated effect. Condit Decl. ¶ 20. Moreover, considering the size of the prior art genus of virulence genes, the number of combinations was so large that one would not be educated towards the claimed combination. Id.

Regarding the secondary references, Zhang et al. 1996; and Paoletti USP 5,942,235 (as further evidenced by P04637); additional to the primary references, Mastrangelo et al. (1995) WO 95/31105 in view of Dorner et al. USP 6,103,244 and further in view of Buller et al. 1988, discussed as the cited prior art in the preceding paragraph: the former secondary reference describes an insert, enhanced green fluorescent protein (EGFP) (Claim 18); and the latter secondary reference describes another insert, a tumor suppressor gene (Claim 12) that is p53 (Claim 13), which itself is said to be considered a suicide gene (Claim 49). The secondary references describing these inserts, and the descriptions in the primary references of other inserts, do not fill in the gap created by the cited prior art, because neither do they provide motivation, considering the size of the prior art genus of virulence genes, to select the claimed TK and VGF double deletion combination. Thus the secondary references describing these inserts, and the description in the primary references of other inserts, cannot assist in the 103 rejection.

Synergism has been demonstrated in McCart et al. 2001, specifically in Fig. 4A, for pathogenicity in animals. Condit Decl. ¶ 22. One can argue from Table 1 that the effects of the mutations on replication are not synergistic but rather additive. Condit Decl. ¶ 23. The combined effect on tumor selectivity, measured in terms of virus replication, was additive.

Appl. No. : 09/991,721
Filed : November 13, 2001

Condit Decl. ¶ 25. Therefore, one would not have predicted a synergistic effect of the double deletion on survival. Id. The lesson is that synergy would not have been predicted from the additive effect on replication, yet synergy for survival did occur. Condit Decl. ¶ 27.

Thus, considering all the factors related to the nonobviousness issue, comparison with the closest prior art, the prior art teaches away (which bars a prima facie case of obviousness), unexpected result of tumor selectivity relative to the prior art (which rebutts a prima facie case of obviousness), comparison with the cited prior art, the showing of synergy, the showing of additivity, and the unpredictability of synergy, it must be concluded that the claims are nonobvious over the references and in compliance with 35 USC 103(a).

CONCLUSION

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of all outstanding rejections are respectfully requested. Allowance of the claims at an early date is solicited. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the below-given telephone number.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 9/28/06

By: 

Nancy W. Vensko
Registration No. 36,298
Attorney of Record
Customer No. 45,311
(805) 547-5580

AMEND

2949685_1
092506